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| EXAMINER |
|---|
| SIEW, JEFFREY |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | 14 |

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/854,417 | Applicant(s) NIKIFOROV ET AL. | |
|---|---|---|---|
| | Examiner Jeffrey Siew | Art Unit 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Double Patenting*

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1,5-11,13-17,22, 23,25-27 & 36-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No.6,436,646 in view of Linn et al (US5,800,989 Sept, 1 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 1,5-11,13-17,22, 23,25-27 & 36-38 are drawn to the method of hybridizing a first nucleic acid and second nucleic acid with a fluorescently labeled probe and detecting FP wherein the fluorescent label is neutral or positively charged.

Claims 1-12 of US 6,436,646 are drawn to the method of hybridizing a fluorescently labeled probe to target nucleic acid and detecting FP, monitoring and SNP detection. Claim 1 further drawn to adding polycation.

Claims 1-12 of US 6,436,646 are not drawn to neutral or positively charged fluorescent label.

Linn et al teach rhodamines which are neutral for FP detection of nucleic acid targets (see col. 9 line 49).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Linn et al's rhodamine dye to the method claims 1-12 of US 6,436,646 in order to provide for a label with an adequate fluorescent time for measuring. Linn et al teach a successful application of rhodamine dye to FP detection and the rhodamine dye provide optimal fluorescent lifetime for successful monitoring (see col. 9 lines 50-60). It would have been prima facie obvious to apply Linn et al's rhodamine dye to the method claims 1-12 of US,6,436,646 in order to provide a dye with an adequate fluorescence lifetime for successful detection.

Moreover, it is noted that claims 1-12 of US6,436,646 are drawn to the additional limitation of using a polycation which would represent a species of the generic method claims of the instant application which do not recite such a limitation (exc. claim 2).

2. Claims 1,2,5-11,13-17,22, 23,25-27,33 & 36-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8,9,10, 21-31 of U.S. Patent No.6,287,774 in view of Linn et al (US5,800,989 Sept, 1 1998). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 1,2,5-11,13-17,22, 23,25-27,33 & 36-38 are drawn to the method of hybridizing a first nucleic acid and second nucleic acid with a fluorescently labeled probe and detecting FP.

Claims 8,9,10,21-31 of US 6,436,646 are drawn to the method of hybridizing a fluorescently labeled probe to target nucleic acid and detecting FP, monitoring. Claim 8 is further drawn to polylysine.

Claims 8,9,10,21-31 of US 6,436,646 are not drawn to neutral or positively charged fluorescent label.

Linn et al teach rhodamines which are neutral for FP detection of nucleic acid targets (see col. 9 line 49).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Linn et al's rhodamine dye to the method claims 8,9,10,21-31 of US 6,436,646 in order to provide for a label with an adequate fluorescent time for measuring. Linn et al teach a successful application of rhodamine dye to FP detection and the rhodamine dye provide optimal fluorescent lifetime for successful monitoring (see col. 9 lines 50-60). It would have been prima facie obvious to apply Linn et al's rhodamine dye to the method claims 9,10,21-31 of US 6,436,646 in order to provide a dye with an adequate fluorescence lifetime for successful detection.

3. The response proposes to address the double patenting rejections until notice of allowable subject matter. At this time no such determination has been made. The double patenting rejections are maintained.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,3-7,9,11, 14-17,22, 23,25, 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Linn et al (US5,641,633 June 24, 1997).

Linn et al teach a hybridization assay for detection by contacting a first nucleic acid with a second oligonucleotide probe with labeled rhodamine and detecting FP (see whole document esp.col. 8 lines 30-col. 9 line 45, col4 line s 50-53 & col.5 lines 3-10). They do not teach adding any polyion. They teach that larger molecules tumble slower than smaller molecules (see col.1 lines 19-26). The oligonucleotides may form double stranded form during hybridization (see col. 9 lines 40-42). They teach end point measurements of FP over real time starting at time 0 and after hybridization 9see col. 9 lines 55-60 & fig. 1). They perform measurements with signal stranded oligonucleotide alone (see col. 10 line 62). They teach detection of target sequence from mycobacterium tuberculosis (see col. 14 line 44).

5. The response filed 2/4/03 has been fully considered and deemed not persuasive. The response states that only mentions the use of rhodamine and texas red dyes to label nucleic acids and applicants had discovered the dramatic improvement of FP signal. Lynn do explicitly teach the use of the rhodamine and texas Red in their method (see col. 9 line 45-50) and give direction as to how to use the dyes in their methods (see col. 9 lines 51-65). More importantly, the dramatic and unexpected improvements would obviate a obviousness rejection and do not overcome the anticipation rejection. Moroever, the response makes a distinction that the

rhodamine dyes may be positive,neutral or negative depending on the salt. The claims do not recite explicitly any limitation of the type of salt form of the dyes. The rejection is maintained.

## *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2,5-11,13-27,33 & 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov (US.6,287,774 Sept. 11, 2001) in view of Linn et al (US5,800,989 Sept, 1 1998).

Nikiforov teaches a method of detecting by contacting a first nucleic acid to second nucleic acid with fluorescent label and detecting FP (see col.11 lines 8-17 & Figure 2). They teach the probe may be PNA (see col.11 line 22). They teach also the addition of polycation such as polylysine (see col.11 lines 49). They teach the detection of SNPs (see col. Example 4) with perfectly complementary probes and with targets with substituted base. They teach binding to

both perfectly complementary and SNP target (see example 3). They teach plotting overtime and histogram (see Figure 15 & 16). Nikiforov teach rotational correctional time (see col.6).

Nikiforov do not explicitly teach neutral or positively charged fluorescent label.

Linn et al teach rhodamines which are neutral for FP detection of nucleic acid targets (see col. 9 line 49).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Linn et al's rhodamine dye to the Nikiforov method in order to provide for a label with an adequate fluorescent time for measuring. Linn et al teach a successful application of rhodamine dye to FP detection and the rhodamine dye provide optimal fluorescent lifetime for successful monitoring (see col. 9 lines 50-60). It would have been prima facie obvious to apply Linn et al's rhodamine dye to the Nikiforov's method in order to provide a dye with an adequate fluorescence lifetime for successful detection.

Moreover, Nikiforov et al teach that the FP rotational correlational time which would allow for real time detection during hybridization, it would have been prima facie obvious to monitor the binding over real time and plot the binding in histogram in order to examine the hybridization kinetics.

Moreover, as it was well known and practiced in the art to construct graphs and histograms to display data, it would have been prima facie obvious to characterize the data in histogram to differentiate the different data points.

7. Claims 12,13, 18-21,24 & 26-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linn et al (US5,641,633 June 24, 1997) in view of Saiki et al (Nature vol. 324 Nov. 1986).

The teachings of Linn et al are described previously.

Linn et al do not teach testing multiple probes.

Saiki et al teach the use of allele specific oligonucletoides which when perfectly match hybridize and detecting mismatches and allelic variations in particular single base mutations (see whole doc. esp. abstract).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Saiki et al's teaching of allele specific probes to Linn et al's FP analysis method in order to detect allelic variation. It would have been prima facie obvious that apply Saiki et al's ASO probes with Linn et al's FP analysis in order to detect mutations including SNPs in real time with greater sensitivity.

Moreover, as it was well known and practiced in the art to construct graphs and histograms to display data, it would have been prima facie obvious to characterize the data in histogram to differentiate the different data points.

8. The response filed 2/4/03 has been fully considered and deeme not persuasive. The response states that the combination of Linn et al and Saiki et al do not describe the invention. The response state that Linn et al would have discriminated during amplification rather than during the FP detection phase. Linn et al do teach the detectionof successful amplification that results in duplex formation. Saiki et al teach the use of ASO probes that only bind to

complementary template with the single base polymorphism and results in successful amplification. One of ordinary skill in the art would have been motivated to simply apply Linn et al's FP analysis which would then discriminate the successful amplification of Saiki et al's ASO probes during the FP detection phase. The rejection is maintained.

9. Claims 8,10 & 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linn et al (US5,641,633 June 24, 1997) in view of Hyldig-Nielsen et al (US6,280,946 Aug. 28, 2001).

The teachings of Linn et al are described previously.

Linn et al do not teach PNAs.

Hyldig-Nielsen et al teach PNA probes for hybridization detection (see whole doc esp. abstract).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Hyldig-Nielsen et al's teaching of PNA probes to Linn et al's FP analysis in order to discriminate sequence variations. Hyldig-Nielsen et al teach the many advantages of PNA probes including stability, long shelf life, independence of ionic strength, and greater efficiency in sequence determination (see col.1 lines 60-col.2 lines 5). It would have been prima facie obvious to apply PNA probes to Linn et al's FP analysis in order to increase the efficiency of sequence discrimination.

10. The response filed 2/4/03 regarding the 103 rejection over Linn et al and Hyldig-Nielsen et al have been considered and deemed not persuasive. The response argues that Linn et al and Hyldig-Nielsen et al are not combinable because PNA is a totally different compound than DNA

and references do not teach that the DNA binding proteins would bind to a PNA-DNA complex. The use of PNA had been well established and commonly practiced in the molecular biology at the time the invention was made. PNAs had been used in probes and primers because they offered greater binding efficiencies and stabilities as described by Hyldig-Nielsen. As the claims read broadly and would encompass the use of primers in Linn et al's amplification assay and Hyldig-Nielsen teach the many advantages of PNA oligonucleotides, there would have been a high expectation of success, the PNA primers would successfully amplify duplexes for later detection by DNA binding proteins in Linn et al's FP assay. The rejection is maintained.

## SUMMARY

11. No claims allowed.

## CONCLUSION

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Tracey Johnson for Art Unit 1637 whose telephone number is (703)-305-2982.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Before Final FAX (703) 872-9306 or After Final FAX (703) 30872-9307.

JEFFREY SIEW
PRIMARY EXAMINER

March 24, 2003